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(54) Title: USE OF NEUROMEDINS U8 AND U25 AS THERAPEUTIC COMPOUNDS

(57) Abstract

The therapeutic use of the neuromedin U family of peptides in the selective reduction of blood flow to the gastrointestinal tract is described. The use neuromedin U to achieve the selective reduction in blood flow to the gastrointestinal tract is used as a method of treating, for example, gastrointestinal bleeding and postprandial hypotension. Neuromedin U is also described for use in the diagnosis of the site of gastrointestinal bleeding.

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Use of neuromedins U8 and U25 as therapeutic compounds.

This invention relates to therapeutic uses for certain compounds and pharmaceutical compositions containing them. In particular it relates to the therapeutic use of neuromedins.

Neuromedins are a family of peptides which have been found in tissue extracts from the brain, spinal cord and gastro-intestinal tract of different species of mammals. The neuromedin family includes two peptides known as neuromedin U-8 (NMU-8) and neuromedin U-25 (NMU-25), neuromedin U-8 constituting the amidated C-terminus of neuromedin U-25. NMU-8 and NMU-25 were first identified in extracts from porcine spinal cord (Minamino et al Biochem. Biophys. Res. Comm. 130 (1985) 1078-1085) and were found to cause uterine contraction and pressor effects in the rat. Subsequent studies have shown that a neuromedin like immunoreactivity is associated with various tissues in the rat, pig, guinea pig and human (Domin, J. et al, Biochem. Biophys. Res. Comm. 140, 1127-1134 (1986).

More recently Sumi et al (Life Sciences, Vol. 41, pp 1585-1590 (1987)) have investigated the effect of synthetic neuromedin U-8 and U-25 on blood flow in portal vein, superior mesenteric artery and pancreatic tissues in anaesthetised dogs. These studies indicated that these peptides had a potent and probably selective activity on splanchnic circulation in anaesthetised dogs and may well be recognised as physiologically significant novel neuropeptides or hormones.

It should be noted, however, that peptide hormones often have differential effects in different animal species, for instance, the differential effects of vasopressin in rats versus dogs. Also the observed effects of peptide hormones in anaesthetised animals may differ markedly from their effects in the same animals when conscious, let alone from one animal species to another.

We have now further investigated NMU-8 and NMU-25 and have discovered that neuromedins have potential for use in therapy, in particular for the selective reduction of blood flow to the gastrointestinal tract.

Accordingly in a first aspect the invention provides a neuromedin U for use in therapy.

The therapy is preferably the selective reduction of blood flow to the gastrointestinal tract.

It is desirable to reduce the blood flow to the gastrointestinal tract as a method of treating for example gastrointestinal bleeding and postprandial hypotension.

Duodenal ulcers and chronic benign gastric ulcers are grouped together as peptic ulcers. Peptic ulcers are breaks in the mucosal lining of the gastrointestinal tract thought to be caused by an imbalance between the damaging effects of acid and pepsin attack and the body's mucosal defences. In cases of severe ulceration the blood vessels supplying the gut are affected, leading to haemorrhaging. Haemorrhage from the stomach and duodenum is the most common life-threatening gastrointestinal emergency. Venous blood from the gastrointestinal tract drains eventually into the portal vein and then passes through the liver. The portal blood pressure rises with increased resistance to portal flow or with an increase in portal blood flow. Portal hypertension is commonly associated with cirrhosis of the liver. As a consequence of the elevated portal venous pressure collaterals may appear which bypass the block and allow portal blood to pass directly into the systemic venous circulation thereby lowering the portal venous pressure. The diverted blood may commonly be passed via collaterals into the vascular plexus of the oesophagus. Serious gastrointestinal bleeding may occur from oesophogeal varices. Gastrointestinal bleeding may also commonly arise, for example, from acute mucosal lesions, vascular malformations and diverticulitis.

In order to be useful in the treatment of gastrointestinal bleeding it is essential that the therapeutic agent is able to preferentially affect the blood vessels supplying the gastrointestinal tract such that the blood supply is reduced selectively at the desired site. A further essential requirement is that the blood supply should be affected without substantially altering the normal blood pressure or adversely affecting the cardiac system.

Gastrointestinal bleeding is commonly treated by administering vasopressin or vasopressin analogues (Soderlund C. Scand. J. Gastroenterol 22 (suppl 137) 50-55 (1987)). These compounds do not, however, show the desired selectivity of action (Bennett et al J. Physiol (Lond) (1988) 398 54P) leading to serious side effects associated with their use such as a reduction in cardiac output, cardiac arrythmia and contraction of the gut. There is, therefore, a real need for an effective therapeutic agent which shows the required selectivity of action.

We have found that it is possible to achieve both the required selectivity of site of action and the desired effect on gastrointestinal blood supply without substantially affecting blood pressure and cardiac performance by administration of an appropriate amount of neuromedin U.

As used herein the term normal blood pressure denotes a blood pressure considered to be within the normal range.

Thus, in a second aspect the invention provides neuromedin U for use in the treatment of gastrointestinal bleeding.

By slowing down the blood flow and allowing a blood clot to form, neuromedin U may also be useful in the diagnosis of the site of gastrointestinal bleeding. For example, the position of the blood clots may be imaged thereby identifying the location of the bleeding.

Thus, in a third aspect the invention provides neuromedin U for use in a method for the diagnosis of the site of gastrointestinal bleeding in a human patient, wherein neuromedin U is administered to the patient, a blood clot is allowed to form and the site of the blood clot is located by imaging or other means.

Postprandial hypotension is caused by the dilatation of blood vessels supplying the gastrointestinal tract following eating. There is no treatment for people suffering from this condition who must lie down after eating to compensate for the fall in blood pressure. This is obviously unsatisfactory and there exists a real need for an effective treatment.

In order to be useful in the treatment of postprandial hypotension, the therapeutic agent must selectively reduce the blood supply to the gastrointestinal tract such that the fall in blood pressure caused by the dilatation of the blood vessels supplying the gastrointestinal tract is reversed and the blood pressure is restored to the pre-feeding level.

Thus, in a fourth aspect the invention provides neuromedin U for use in the treatment of postprandial hypotension.

As used herein the term neuromedin U includes any neuromedin U, preferably a mammalian neuromedin U and most especially porcine or human neuromedin U and also biologically active fragments, analogues and derivatives thereof which have the characteristic properties of neuromedin U, i.e. which preferably act on the gastrointestinal bed to differentially affect gastrointestinal blood flow without substantially affecting normal blood pressure and cardiac performance. The fragments, analogues and derivatives may be naturally occurring or may be produced chemically e.g. by chemical modification, cleavage, or synthesis or they may be produced by employing recombinant DNA techniques. The analogues and derivatives may include non-peptide compounds as well as peptide

compounds. The neuromedin is preferably NMU-8 or NMU-25 or rat neuromedin. The use of human neuromedin, e.g. human NMU-8 or human NMU-25, is especially preferred.

Thus, the amino acid sequences of porcine NMU-8 and NMU-25 are as follows:

NMU-8 Tyr-Phe-Leu-Phe-Arg-Pro-Arg-Asn-NH_2

NMU-25 Phe-Lys-Val-Asp-Glu-Glu-Phe-Gln-Gly-Pro-Ile-Val-Ser-Gln-Asn-Arg-Arg-Tyr-Phe-Leu-Phe-Arg-Pro-Arg-Asn-NH_2

Natural Neuromedin Us of other mammalian species and useful peptide fragments, analogues and derivatives thereof will typically have significant homology e.g. at least 70%, preferably at least 75% and often at least 80% or more homology, with the above identified porcine sequences or relevant portions thereof. Suitable analogues may have sequences similar to the porcine sequence but for suitable substitution of amino acid residues, for example substitution of one acidic or hydrophilic amino acid residue for another acidic or hydrophilic amino acid residue of similar size.

Rat neuromedin has also been described in the literature (Conlon et al; J. Neurochem 51, 988-991 (1988), and this neuromedin as well as appropriate fragments and analogues thereof may be used as the neuromedin U of the present invention.

The neuromedin U may be isolated from the appropriate mammalian tissue such as the porcine spinal cord and purified using conventional protein purification techniques. Conveniently the neuromedin U may be synthesised using well known peptide synthetic methods (e.g. the Merrifield solid phase peptide synthesis or the so-called FMOC procedure (see "Solid Phase Peptide Synthesis - A Reassessment" by R.C. Sheppard - from Molecular Endocrinology eds MacIntyre and Szelke Elsevier (1977) P43-56; E. Atherton et al J.C.S. Chem. Comm (1981) P1151-1152; and G. Barany and R.B. Merrifield in "The Peptides" eds E. Gross and J. Jeinehofer,

Academic Press, New York (1980) P3). Chemically synthesised neuromedin U may be purified using conventional techniques such as chromatography.

The published amino acid sequence of the porcine neuromedin Us may be used to identify other homologous mammalian neuromedin Us using techniques well known in the art, for example as described in Maniatis et al (1982) "Molecular Cloning - A Laboratory Manual" Cold Spring Harbour Laboratory. cDNA clone banks may be made from mRNA prepared from mammalian tissue which produces the neuromedin U. A gene encoding a mammalian neuromedin U may then be identified by probing the cDNA banks with labelled DNA probes based on the N-terminus amino acid sequence of porcine neuromedin U. Provided appropriate hybridisation conditions are used, the labelled probes will hybridise to sufficiently homologous mammalian genes. Once identified the gene encoding the neuromedin U may be inserted into an appropriate vector for expression in bacterial, yeast or mammalian cells. Suitable vectors include for example those described in British Patent No. 2136814B.

It is envisaged that neuromedin U may be particularly useful in the treatment of gastrointestinal bleeding which is associated with cirrhosis and peptic ulcers.

Thus in a fifth aspect the invention provides a method of selectively reducing the blood flow to the gastrointestinal tract which comprises administering an effective amount of neuromedin U.

Typically the amount of neuromedin U used is an amount which is effective in differentially decreasing gastrointestinal blood supply without substantially affecting normal blood pressure and cardiac performance.

Furthermore, in a sixth aspect the invention provides a pharmaceutical composition for use in the selective reduction of blood flow to the gut comprising neuromedin U, in combination with a pharmaceutically acceptable diluent, carrier or excipient.

In a preferred embodiment of the sixth aspect, the invention provides a pharmaceutical composition in unit dosage form, each unit dose comprising an amount of neuromedin U sufficient to differentially decrease the gastro-intestinal blood supply without substantially affecting normal blood pressure and cardiac performance.

In a seventh aspect the invention provides a process for the production of a pharmaceutical composition according to the sixth aspect of the invention comprising bringing a neuromedin U into association with a pharmaceutically acceptable carrier, excipient or diluent.

In a eighth aspect the invention provides the use of neuromedin U for the manufacture of a medicament for the treatment of gastrointestinal bleeding.

Pharmaceutical compositions for use according to the present invention may be formulated in conventional manner, optionally with one or more physiologically acceptable carriers, excipients or diluents. Neuromedin Us for use according to the present invention may be formulated for oral, buccal, parenteral or rectal administration or in a form suitable for nasal administration or administered by inhalation or insufflation.

For oral administration, the pharmaceutical compositions may take the form of, for example, tablets or capsules prepared by conventional means with pharmaceutically acceptable excipients such as binding agents (e.g. pregelatinised maize starch, polyvinylpyrrolidone or hydroxypropyl methylcellulose); fillers (e.g. lactose, microcrystalline cellulose or calcium hydrogen phosphate); lubricants (e.g. magnesium stearate, talc or silica); disintegrants (e.g. potato starch or sodium glycollate); or wetting agents (e.g sodium lauryl sulphate). The tablets may be coated by methods well known in the art. Liquid preparations for oral administration may take the form of, for example, solutions, syrups or suspensions, or they may be presented as a dry product for

constitution with water or other suitable vehicle before use. Such liquid preparations may be prepared by conventional means with pharmaceutically acceptable additives such as suspending agents emulsifying agents, non-aqueous vehicles and preservatives. The preparations may also contain buffer salts, flavouring, colouring and sweetening agents as appropriate. Preparations for oral administration may be suitably formulated to give controlled release of the active compound.

For buccal administration the compositions may take the form of tablets or lozenges formulated in conventional manner.

The neuromedin U may be formulated for parenteral administration by injection e.g. by bolus injection or continuous infusion. Formulations for injection may be presented in unit dosage form. The compositions may take such forms as suspensions, solutions or emulsions in oily or aqueous vehicles, and may contain formulatory agents such as suspending, stabilising and/or dispersing agents. Alternatively, the active ingredient may be in powder form for constitution with a suitable vehicle, e.g. sterile pyrogen-free water, before use.

The neuromedin U may also be formulated in rectal compositions such as suppositories or retention enemas, e.g. containing conventional suppository bases such as cocoa butter or other glycerides.

In addition to the formulations described previously, the compounds may also be formulated as a depot preparation. Such long acting formulations may be administered by implantation or by intramuscular injection.

For administration by inhalation the compounds for use according to the present invention are conveniently delivered in the form of an aerosol spray presentation from pressurised packs or a nebuliser, with the use of a suitable propellant, e.g. dichlorodifluoromethane, trichlorofuloromethane, dichlorotetrafluoroethane, carbon dioxide or other suitable gas.

The compositions may, if desired, be presented in a pack or dispenser device which may contain one or more unit dosage forms containing the active ingredient. The pack or dispenser device may be accompanied by instructions for administration.

The dose at which the neuromedin U will be administered to man will be such that the gastrointestinal blood supply is differentially decreased and normal blood pressure and cardiac performance are not substantially affected. The precise dose of neuromedin U will depend upon the route of administration, the potency of the neuromedin U and the body weight of the patient. For example, NMU-8 may be administered to an average 70kg man by IV infusion at doses in the range 0.01µg/min to 1.5µg/min over a time period of 60 minutes and NMU-25 may be administered to an average 70kg man by IV infusion at dose in the range 0.05µg/min to 5.00µg/min over a time period of 60 minutes. In a typical IV infusion the lowest dose is administered for a period of 10 minutes and this dose is then doubled every ten minutes until the desired effect is seen up to a maximum of 1.5µg/min. The total of neuromedin administered may be up to 22.25µg which may be administered twice a day.

The invention is further illustrated in the following examples and with reference to the following figures in which:

Figure 1: shows the cardiovascular responses to bolus injections of 0.1nmol and 1.0nmol NMU-8 in the same conscious rat.

Figure 2: shows the cardiovascular responses to bolus injections of 0.01nmol, 0.1nmol and 1.0nmol NMU-25 in the same conscious rat.

Figure 3: shows the cardiovascular changes at the onset of NMU-8 infusion (10nmol/h) in a conscious rat.

Figure 4: shows the cardiovascular changes at the end of a 60 min infusion of NMU-8 (10nmol/h) in a conscious rat.

Figure 5: shows the cardiovascular changes at the onset and offset of a 1h infusion of NMU-25 in a conscious rat.

Example 1

Investigation of the effect of porcine NMU-8 and NMU-25 on cardiovascular responses in rats

Animals were anaesthetised (sodium methohexitone, 60mg/kg i.p.) and had miniaturised, pulsed Doppler probes implanted around the left renal and the superior mesenteric arteries and the distal abdominal aorta, below the level of the ileocaecal artery (this probe is thus positioned to monitor hindquarters flow). The wires from the probes were tunnelled subcutaneously and exited at the back of the neck through a small incision, where they were anchored to the skin with their ends free. Animals were allowed to recover for at least 7 days with access to food and water.

Subsequently rats with acceptable signals from all 3 probes (n=6-8) were briefly re-anaesthetised (sodium methohexitone, 40mg/kg i.p.) and had an intravenous and an intra-arterial (abdominal aorta via the caudal artery) catheter implanted. These catheters were tunnelled subcutaneously and exited at the same point as the Doppler probe wires. The latter were soldered into a micro-connector that was clamped into a harness fitted to the rat. This same harness was connected to a flexible spring through which the catheters ran, for protection. The following day continuous recordings were made of BP and instantaneous heart rate (HR) and Doppler shift signals from all 3 probes. It has been shown that the latter are a good index of volume flow, and from these signals and the BP recording, % changes in regional vascular resistances were calculated.

Administration of vehicle (isotonic saline containing 1% bovine serum albumin) was without systematic effect on cardiovascular variables. Bolus injection of porcine NMU-8 (0.1nmol) caused a slight, transient, increase in BP (Figure 1) accompanied by superior mesenteric vasoconstriction with no other regional haemodynamic changes (Figure 1). As reported by Minamino et al (Biochem. Biophys. Res. Comm 130 (1985) 1078-1085) bolus injection of 1.0nmol

(i.e. about 3nmol/kg) of porcine NMU-8 caused an increase in BP; this effect was accompanied by a clear reduction in superior mesenteric blood flow but only a small fall in renal blood flow and a slight tachycardia. Similar, selective effects on mesenteric flow were seen with porcine NMU-25, but this peptide was more potent than porcine NMU-8 (Figure 2).

Infusion of NMU-8 (1nmol/h) reduced superior mesenteric blood flow and increased resistance without any significant changes in other variables. At the onset of a 1h infusion of NMU-8 at the higher dose of 10nmol/h there was a transient increase in BP that was accompanied by a reduction in superior mesenteric blood flow (Figure 3).

Calculated resistances increased in renal, mesenteric and hindquarters vascular beds. However, after 60 min of infusion, only the superior mesenteric vascular bed showed a reduction in flow, and this reversed to a significant hyperaemia within 1 min of stopping the infusion (Figure 4). The effects of NMU-25 infusion were more marked than those of NMU-8 (Figure 5).

From the present results it seems that the pressor effects of NMU-8 and NMU-25 as first described by Minamino et al (J. loc cit) were associated with a particularly marked superior mesenteric vasoconstriction, but with no change in hindquarters vascular resistance (or in our experiments, any signs of reflex bradycardia). We have found that lower bolus doses, or infusions of NMU-8 or NMU-25 have selective effects on superior mesenteric blood flow.

Example 2

Investigation of the effect of rat NMU on cardiovascular responses in rats

Rats (n=8) with pulsed Doppler probes received bolus doses of rat NMU (Conlon et al; J. Neurochem 51 988-991 (1988)) (0.001, 0.01 and 0.1nmol) and a 20 min infusion (at 10 nmol/h) of this peptide. The protocol was essentially as described in Example 1. The bolus doses and infusion times for rat NMU were less than for porcine NMU-25 because only a small amount of the former peptide was available.

Measurements were made over the 1 min immediately preceding any intervention and at the time of maximum response following bolus injections; this corresponded to about 0.5 min post-injection. Responses to infusions were assessed from the changes occurring about 5 min after the onset of infusion and at the end of the infusion. The changes after infusion were measured at 5 and 20 min after the offset. All data were analysed by non-parametric, two-way analysis of variance (Friedman's test), Wilcoxon's rank sum test or the Mann-Whitney U test as appropriate.

Bolus doses of rat NMU (Table 1) had effects similar to those seen with porcine NMU-25. Infusion of rat NMU caused increases in BP and HR accompanied by reduction in mesenteric blood flow (Table 2). After the offset of the 20 min infusion of rat NMU there was no mesenteric hyperaemia (Table 2).

Table 1: Peak (about 0.5 min) cardiovascular changes following bolus doses of rat NMU in conscious, Long Evans rats (mean (S.E.M.); n=8)

	0.001 nmol	0.01 nmol	0.1 nmol
Mean BP (mmHg)	1 (1)	3 (1)*	10 (1)*
Heart rate (b/min)	1 (5)	20 (12)	17 (6)*
Doppler shift (%)			
Renal	-1 (1)	-3 (2)	-5 (1)*
Mesenteric	-8 (4)*	-32 (3)*	-36 (5)*
Hindquarters	9 (6)	18 (7)	8 (5)
Vascular resistance (%)			
Renal	2 (2)	7 (4)	15 (2)*
Mesenteric	12 (6)	53 (9)*	81 (17)*
Hindquarters	-6 (4)	-10 (6)	4 (5)

*P < 0.05 compared to baseline (Wilcoxon test)

Table 2: Cardiovascular changes during and after infusion of rat neuromedin (10 nmol/h) in conscious, Long Evans rats (mean (S.E.M.); n=8)

	During		After	
	5 min	20 min	5 min	20 min
Mean BP (mmHg)	8 (1)*	10 (2)*	7 (2)*	3 (2)
Heart rate (b/min)	25 (12)	25 (6)*	40 (13)*	13 (7)
Doppler shift (%)				
Renal	-1 (1)	4 (3)	8 (2)*	5 (3)
Mesenteric	-27 (4)*	-19 (4)*	-10 (4)	-7 (3)
Hindquarters	-5 (7)	-8 (4)	-6 (5)	-9 (5)
Vascular resistance (%)				
Renal	10 (3)*	7 (3)	0 (3)	-1 (4)
Mesenteric	50 (9)*	40 (8)*	20 (6)*	12 (5)
Hindquarters	18 (10)	22 (5)*	16 (6)	15 (5)

*$P < 0.05$ compared to baseline (Friedman's test)

We have found that low bolus doses or infusions of porcine NMU-8, NMU-25 or rat NMU have selective effects on superior mesenteric blood flow. These effects were due to active vasoconstriction (rather than to an autoregulatory response to the change in pressure (Meininger et al; (1988) Am J. Physiol 254 H709-H718) because superior mesenteric blood flow was reduced below baseline. However, since neither renal nor hindquarters blood flows were significantly affected by infusions of NMU-8 or -25 or rat NMU at 10nmol/h, it is likely that any increases in calculated renal and hindquarters vascular resistances under these conditions were autoregulatory (Meininger et al J. loc cit.).

The post-infusion superior mesenteric vasodilatation seen with NMU-8 and NMU-25 must have been active (or 'reactive'), rather than autoregulatory, because it was accompanied by substantial increases in blood flow above baseline levels, whereas the associated fall in calculated renal vascular resistance (following NMU-8) was probably a local regulatory response because flow was not different from baseline at that time. It is likely that the post-infusion hyperaemia was a consequence of the prolonged superior mesenteric hypoperfusion during the 60 min infusion of NMU-8 or NMU-25, since it did not occur following the briefer infusion (20 min) of rat NMU. Since the effects of bolus doses of porcine NMU-25 and rat NMU were similar it appears that the differences in the sequences of these two peptides do not affect their cardiovascular activity, at least in the rat.

We have observed that cardiac output could be reduced by bolus doses of NMU-25 that did not cause bradycardia indicating the cardiac effect might have been due to the increase in afterload, rather than baroreflex effects.

Another neuropeptide that has marked superior mesenteric vasoconstrictor effects in conscious rats is vasopressin. However, administration of exogenous vasopressin, sufficient to cause a pressor effect, (or at lesser doses), does not pick out the superior

mesenteric circulation in the way described here for NMU-8 or NMU-25 or rat NMU, since vasopressin also causes a marked reduction in hindquarters blood flow, and, moreover, elicits a substantial bradycardia. In spite of the side effects of vasopressin administration and the lack of evidence of a beneficial outcome, this manoeuvre is widely used in the acute treatment of the complications of cirrhosis. The present results raise the possibility that rat NMU, NMU-8 or NMU-25 might be more useful than vasopressin (or its analogues) in this clinical context, since they can cause substantial and selective reductions in superior mesenteric blood flow without an increase in systemic arterial BP or any adverse cardiac effects, at least as judged by the absence of arrhythmias or bradycardia.

CLAIMS

1. A neuromedin U for use in therapy

2. A neuromedin U for use in the selective reduction of blood flow to the gastrointestinal tract

3. A neuromedin U for use in the treatment of gastrointestinal bleeding and postprandial hypotension.

4. A neuromedin U for use in a method for the diagnosis of the site of gastrointestinal bleeding in a human patient, wherein neuromedin U is administered to the patient, a blood clot is allowed to form and the site of the blood clot is located by imaging or other means.

5. A method of selectively reducing the blood flow to the gastrointestinal tract which comprises administering an effective amount of neuromedin U.

6. A pharamaceutical composition for use in the selective reduction of blood flow to the gastrointestinal tract comprising neuromedin U in combination with a pharmaceutically acceptable diluent, carrier or excipient.

7. A pharmaceutical composition according to claim 6 in unit dosage form, each unit dose comprising an amount of neuromedin U sufficient to differentially decrease the gastrointestinal blood supply without substantially affecting normal blood pressure and cardiac performance.

8. A process for the production of a pharmaceutical composition according to claims 6 comprising bringing neuromedin U into association with a pharmaceutically acceptable carrier, excipient or diluent.

9. The use of neuromedin U for the manufacture of a medicament for the treatment of gastrointestinal bleeding.

10. A drug for selectively reducing gastrointestinal blood supply containing neuromedin U as active ingredient.

11. A selective gastrointestinal blood supply reducer comprising neuromedin U.

12. A method for selectively reducing blood supply to the gastrointestinal tract which comprises administering to a patient a neuromedin U.

CARDIOVASCULAR RESPONSES TO BOLUS INJECTION OF NEUROMEDIN U8 IN A CONSCIOUS, LONG EVANS RAT

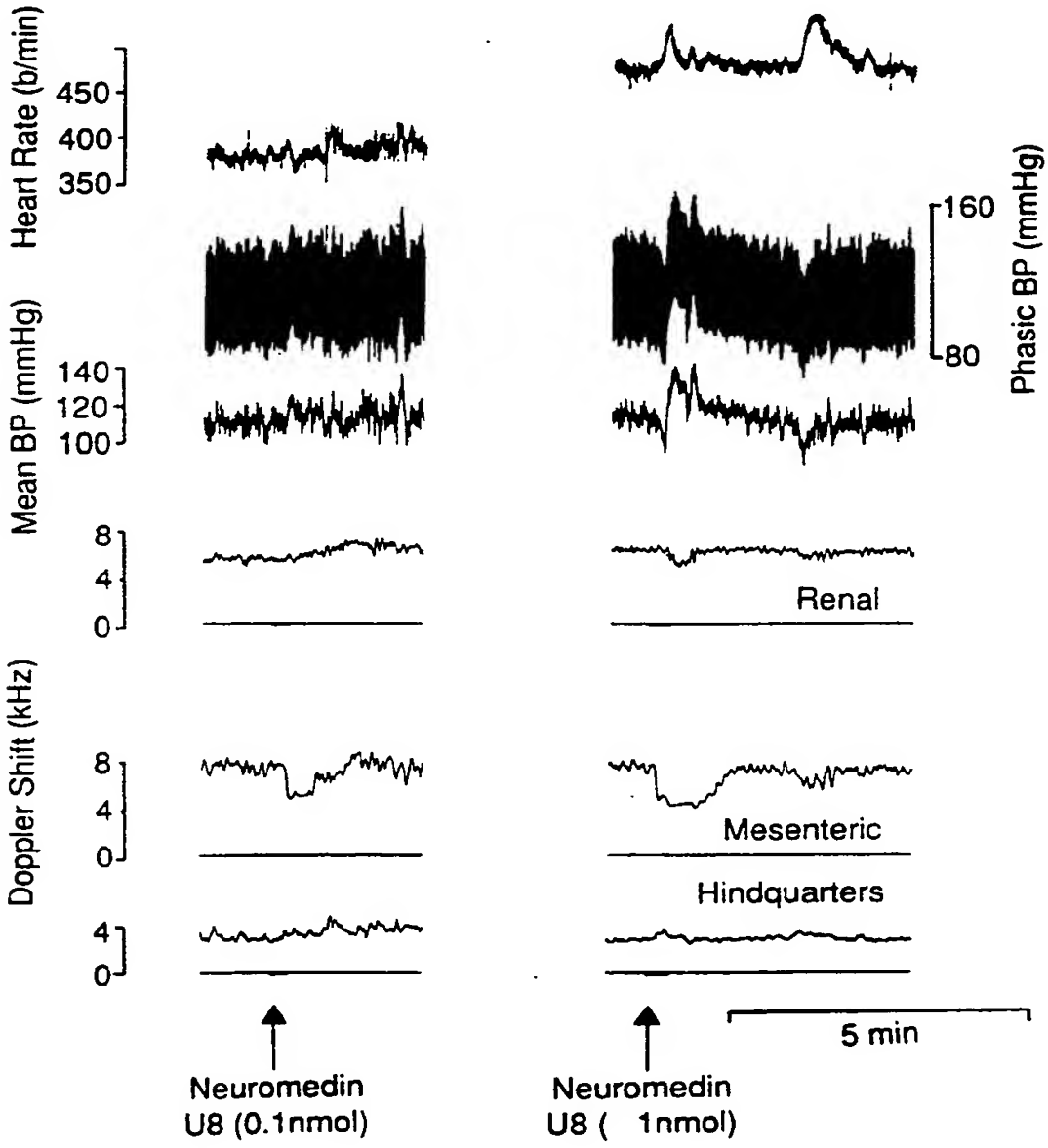
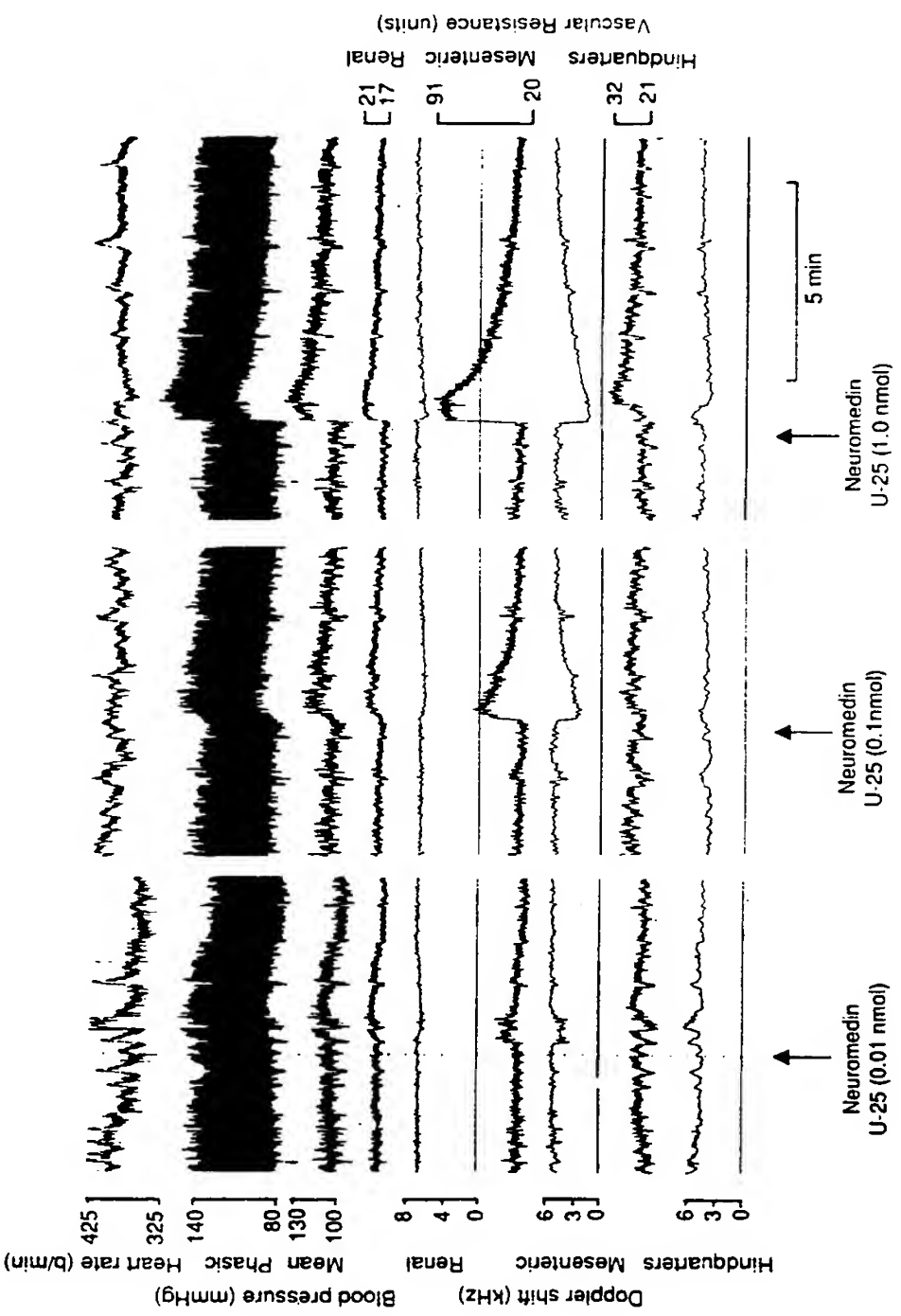


Fig. 1

Fig. 2

CARDIOVASCULAR RESPONSES TO BOLUS INJECTIONS
OF NEUROMEDIN U-25 IN A CONSCIOUS, LONG EVANS RAT



CARDIOVASCULAR CHANGES AT THE ONSET OF INFUSION OF NEUROMEDIN U8 IN A CONSCIOUS, LONG EVANS RAT

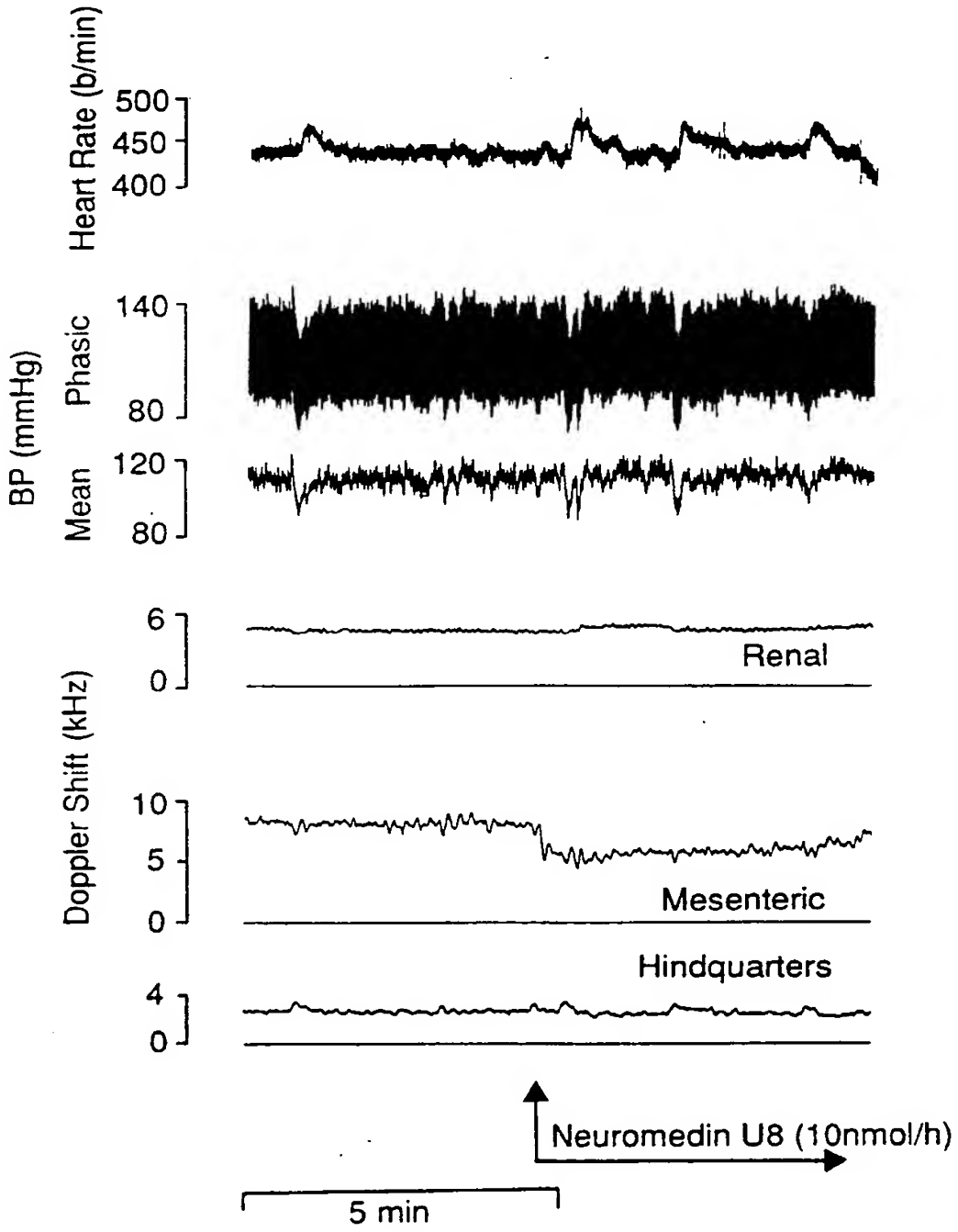


Fig. 3

CARDIOVASCULAR CHANGES AT THE END OF A 1H INFUSION OF NEUROMEDIN U8

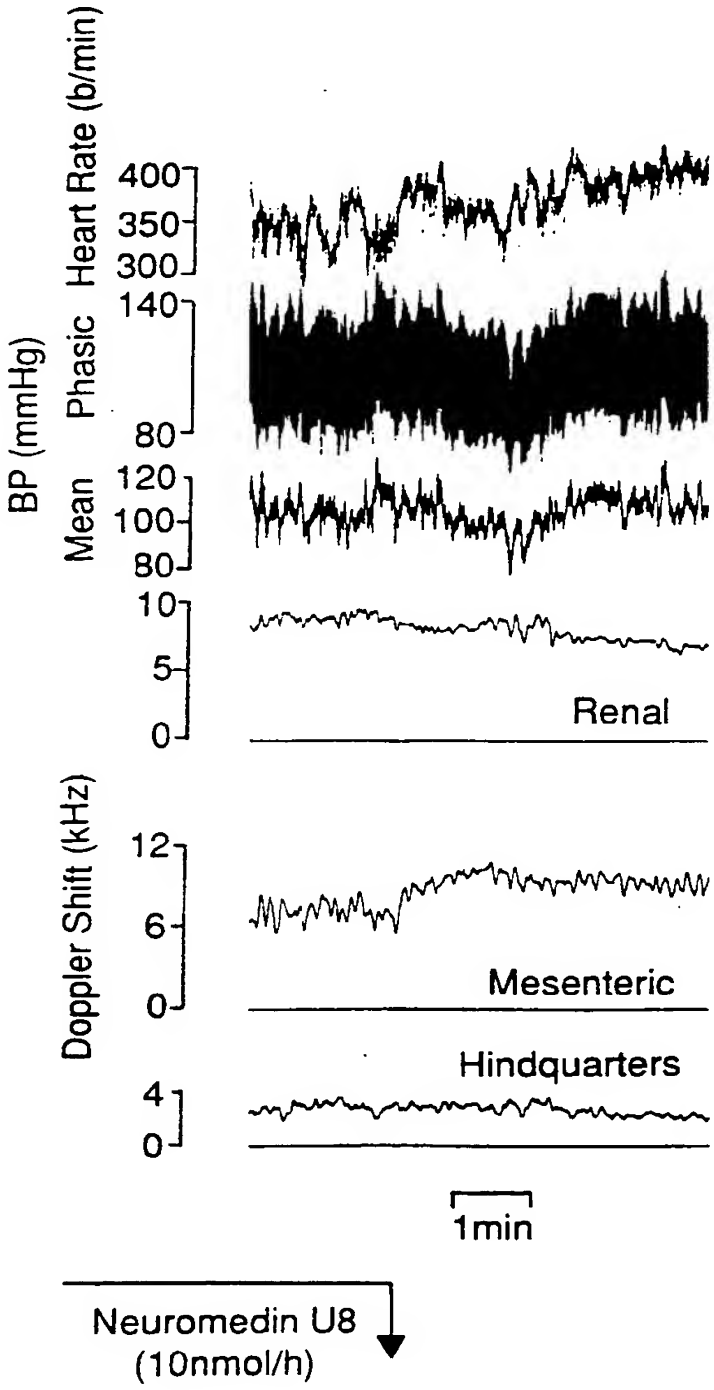
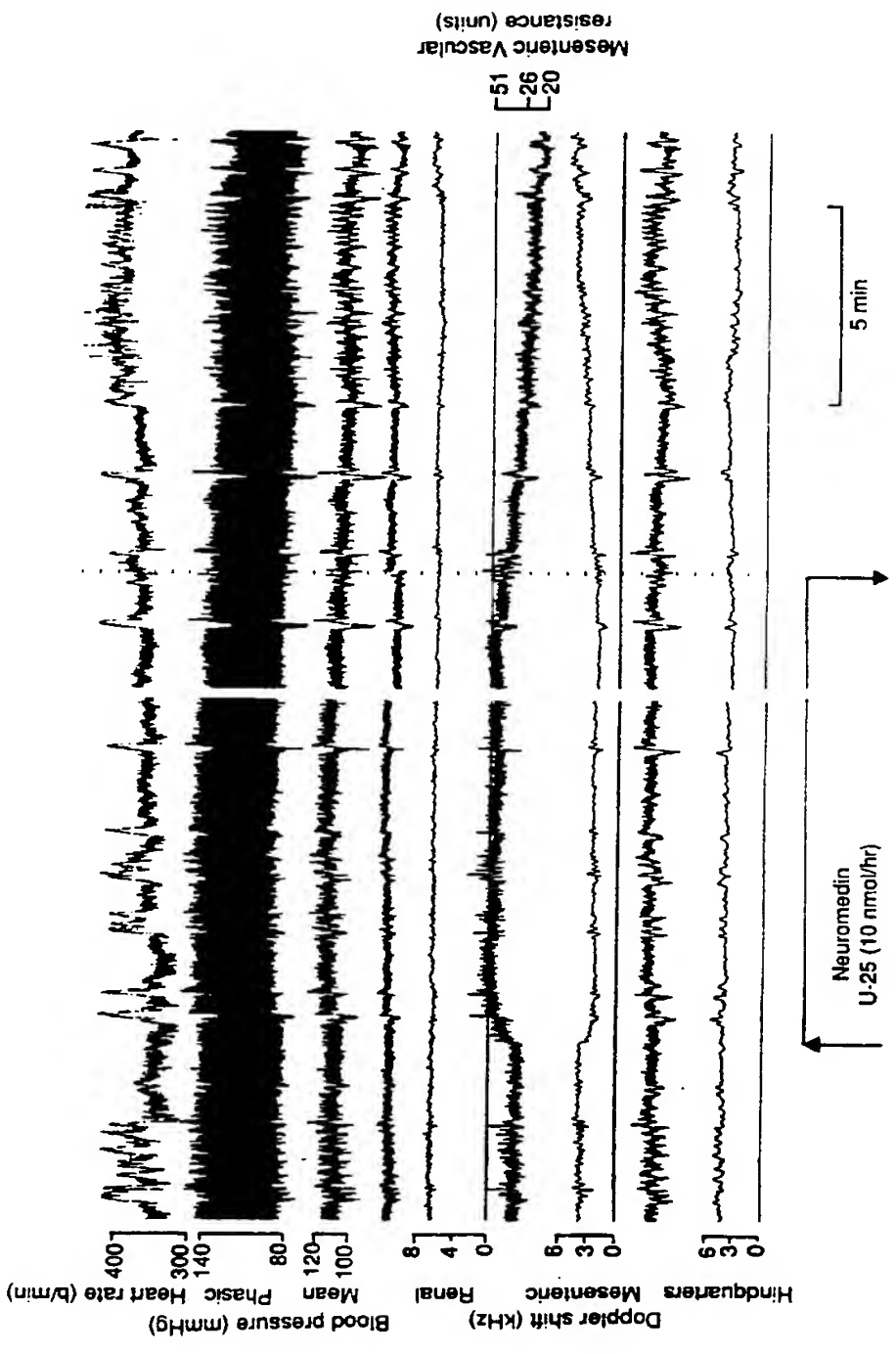


Fig. 4

Fig. 5

CARDIOVASCULAR RESPONSES AT THE ONSET AND OFFSET OF A 1H INFUSION OF NEUROMEDIN U-25 IN A CONSCIOUS, LONG EVANS RAT



INTERNATIONAL SEARCH REPORT

International Application No PCT/GB 89/00924

I. CLASSIFICATION OF SUBJECT MATTER (if several classification symbols apply, indicate all) [6]

According to International Patent Classification (IPC) or to both National Classification and IPC

IPC[5]: A 61 K 37/34, A 61 K 37/02, A 61 K 49/00, C 07 K 7/08

II. FIELDS SEARCHED

Minimum Documentation Searched [7]

Classification System	Classification Symbols
IPC[5]	A 61 K, C 07 K

Documentation Searched other than Minimum Documentation to the Extent that such Documents are included in the Fields Searched [8]

III. DOCUMENTS CONSIDERED TO BE RELEVANT [9]

Category [10]	Citation of Document, [11] with indication, where appropriate, of the relevant passages [12]	Relevant to Claim No. [13]
X	Life Science, volume 41, 1987, Pergamon Journals Ltd, (US), S. Sumi et al.: "Effect of synthetic neuromedin U-8 and U-25, novel peptides identified in procine spinal cord, on splanchnic circulation in dogs", pages 1585-1590 see the whole article cited in the application --	1-3,6-11
Y	Biochemical and Biophysical Research Communications, volume 140, no. 3, 14 November 1986, Academic Press, Inc., J. Domin et al.: "Characterization of neuromedin U like immunoreactivity in rat, porcine guinea-pig and human tissue extracts using a specific radioimmuno-assay", pages 1127-1134 see the whole article cited in the application --	1-3,6-11

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* Special categories of cited documents: [10]

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

IV. CERTIFICATION

Date of the Actual Completion of the International Search	Date of Mailing of this International Search Report
31st Octobe r1989	05. 12. 89

International Searching Authority	Signature of Authorized Officer
EUROPEAN PATENT OFFICE	F.M. VRIJDAG

Form PCT/ISA/210 (second sheet) (January 1985)

FURTHER INFORMATION CONTINUED FROM THE SECOND SHEET

V. [X] OBSERVATIONS WHERE CERTAIN CLAIMS WERE FOUND UNSEARCHABLE [1]

This international search report has not been established in respect of certain claims under Article 17(2) (a) for the following reasons:

1. [X] Claim numbers ....*..... because they relate to subject matter not required to be searched by this Authority, namely:

* Claim numbers 4, 5, 12:
See PCT Rule 39.1.iv:
Methods for treatment of the human or animal body by surgery or therapy, as well as diagnostic methods.

2. [ ] Claim numbers ....., because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:

3. [ ] Claim numbers....., because they are dependent claims and are not drafted in accordance with the second and third sentences of PCT Rule 6.4(a).

VI. [ ] OBSERVATIONS WHERE UNITY OF INVENTION IS LACKING [2]

This International Searching Authority found multiple inventions in this international application as follows:

1. [ ] As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims of the international application.

2. [ ] As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims of the international application for which fees were paid, specifically claims:

3. [ ] No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claim numbers:

4. [ ] As all searchable claims could be searched without effort justifying an additional fee, the International Searching Authority did not invite payment of any additional fee.

Remark on Protest

[ ] The additional search fees were accompanied by applicant's protest.

[ ] No protest accompanied the payment of additional search fees.